REMARKS

Reconsideration of this application is requested. Claims 4-9, 12-23, 26 and 28-36 are in the case.

I. PRIORITY

The comments appearing on page 2 in paragraph 1 have been noted. The specification has been amended to include a sentence along the lines suggested by the Examiner.

II. THE 35 U.S.C. § 112, SECOND PARAGRAPH REJECTION

Claims 1-37 stands rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for the reasons detailed on pages 3 and 4 of the Action. The claims have been amended in response to this rejection. The following comments are offered.

In subparagraph (a) the term "derivative" has been objected to as allegedly indefinite. In response, the expression "pharmaceutically acceptable derivative thereof" has been canceled without prejudice and replaced by "salt, solvate or protective derivative". Basis for this amendment appears, for example, at page 7, line 27 and page 38, lines 18-28. No new matter is entered.

The objection relating to the word "derivative" is directed to "claims 1-37". However, the word "derivative" does not appear in claims 2-24. It is unclear whether the rejection extends to "protected derivative" appearing in claim 25. It is

the Applicants position that no indefiniteness arises with respect to the term "protected derivative", since that expression would be completely clear to one of ordinary skill in this art. That is, a person of ordinary skill would appreciate that a protected derivative of a compound of Formula I would be a compound that can be converted, in a simple deprotection step, to a compound of Formula I. Moreover, the person of ordinary skill would be well aware of the large number of protective groups that may be employed to protect the functional groups present in the compounds of Formula I (such as the protective groups disclosed in the books mentioned at page 37, line 27 to page 38, line 2 of the application as originally filed. If Applicants were forced to specify the exact structures of the protected compounds used in step (z) of claim 25, the claim would no longer provide the Applicants with adequate protection for the invention. Any one of ordinary skill based on the disclosure and level of ordinary skill in this art would be able to easily circumvent such a limited claim thereby rendering it useless to the Applicants. Reconsideration of the objection to the word "derivative" appearing in the claims in this application is accordingly respectfully requested.

In subparagraph (b) claim 6 has been objected to in that there is allegedly insufficient antecedent basis for the limitation "and/or interrupted by an O atom". This objection is respectfully traversed. The definition of "alkyl" provided at page 8, line 22 through page 9, line 3 explicitly covers the compounds mentioned in claim 6. Similar comments apply with respect to claim 11 objected to in subparagraph (c). Withdrawal of the formal points raised in subparagraphs (b) and (c) is accordingly respectfully requested.

With reference to subparagraph (d), claim 16 has been amended to delete the preferred statement. That aspect of the claim is now presented as new dependent claim 38. No new matter is entered.

With regard to subparagraph (e), (f) and (g), claims 19-23 have been canceled without prejudice. Withdrawal of those aspects of the formal rejection are accordingly respectfully requested.

With reference to subparagraph (h), claim 24 has been rejected as allegedly indefinite in that it is allegedly not known what is meant by a person "susceptible to". In response, the phrase objected to would be clear to one of ordinary skill in this art. Thus, antiarrhythmic drugs have often been administered on a prophylactic basis (as was done in the Cardiac Arrhythmia Suppression Trial - see page 1, lines 20-26 of the application as originally filed) to patients who, in the clinical judgment of a physician, are likely to develop an arrhythmia. Thus, one of ordinary skill would be well used to determining which patients are "susceptible to" an arrhythmia.

In subparagraph (i), the term "derivative" in claims 26-37 has been objected to as implying more than what is positively recited. In response, the term "protected derivative" would be completely clear to one of ordinary skill in this art. Thus, one of ordinary skill would appreciate that a protective group has to serve the function of preventing, under certain conditions, reaction of the functional group that it is intended to protect. Moreover, one of ordinary skill would also appreciate that, for a group to properly function as a protective group, it must be possible to insert and remove that group under conditions that will not cause

unwanted reaction of degradation of the molecule to be protected. The application as filed identifies, either directly or by way of reference (see page 30, lines 8-16 and 24-27) many examples of protective groups. A person of ordinary skill would know, or would be able to ascertain by routine and non-inventive methods, which compounds are "protected derivatives" of the compounds of claims 26-34. Similar comments as those made above apply to claims 25-37.

Withdrawal of the outstanding formal rejection is now believed to be in order. Such action is respectfully requested.

III. THE 35 U.S.C. § 101 REJECTION

Claims 22 and 23 stand rejected under 35 U.S.C. § 101 for reasons stated on page 5 of the Action. In response, claims 22 and 23 have been canceled without prejudice.

IV. THE ANTICIPATION REJECTION

Claim 26 stands rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Yamawaki et al, Garrison et al, U.S. Patent 5,576, 327 to Schoen et al, U.S. Patent 4,912,113 to Schoen et al and U.S. Patent 4,906,640 to Schoen et al. In response to those rejections, and without conceding to the merit of the positions taken by the Examiner, Claim 26 has been amended to add "or C_1-C_6 alkyl" at the end of the claim. This amendment deletes C_1-C_6 alkyl from the definition R^7. Compounds as now claimed in Claim 26 are not anticipated by any of the

references relied on by the Examiner. Withdrawal of the outstanding anticipation rejections is accordingly respectfully requested.

V. THE OBVIOUSNESS REJECTION

Claim 26 stands rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent 5,576,327 Schoen et al. That rejection is respectfully traversed.

As noted above, Claim 26 has been amended to remove C_1-C_6 alkyl from the definition of R^7. None of the Schoen et al patents discloses or suggests compounds of Formula II in which R^7 represents aryl (other than phenyl) or heterocyclic.

VI. DOUBLE PATENTING

Claim 26 stands provisionally rejected on obviousness-type double patenting grounds over co-pending application Serial No. 09/623,705. That rejection is respectfully traversed. Claim 26 of the present differs from Claim 21 of Serial No. 09/623,705 in that the latter claim relates to compounds of formula II in which the group equivalent to R^7 represents optionally substituted phenyl only. Such compounds are expressly excluded from the scope of Claim 26 of the present case. Withdrawal of the obviousness-type double patenting rejection is accordingly respectfully requested.

VII. FORMAL MATTERS

It has recently been discovered that when the PCT application from which the present case derives was filed at the Swedish Receiving Office, it erroneously included an additional page 56 from co-pending application PCT/SE00/01252 (which corresponds to US 09/623,705, Attorney Ref: 3525-95) (i.e. two page 56's were in the PCT case, one which was the correct page 56 and the second which was the erroneous page 56). The U.S. national stage case which was filed was correct in that it did not contain the erroneous page 56. Attention is being drawn to this informality so that no question of non-disclosure arises.

In order to avoid possible overlap with the disclosures of prior art documents such as US 3,962,449 (copy enclosed with a PTO 1449 , see Table 3 and Claim 1 of that document), "C_{1-6} alkyl" has been deleted without prejudice from the definition of R^7 in Claim 33.

The number *"655 228"* has been amended such that it reads *"665 228"* (see page 2, line 15 of the application as filed). This corrects an obvious error and no new matter is entered.

Allowance of the application is awaited.

Respectfully submitted,

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VERSION WITH MARKINGS SHOWING CHANGES MADE

IN THE SPECIFICATION

Please cancel the paragraph at page 2, lines 13-28 and replace by the following amended paragraph.

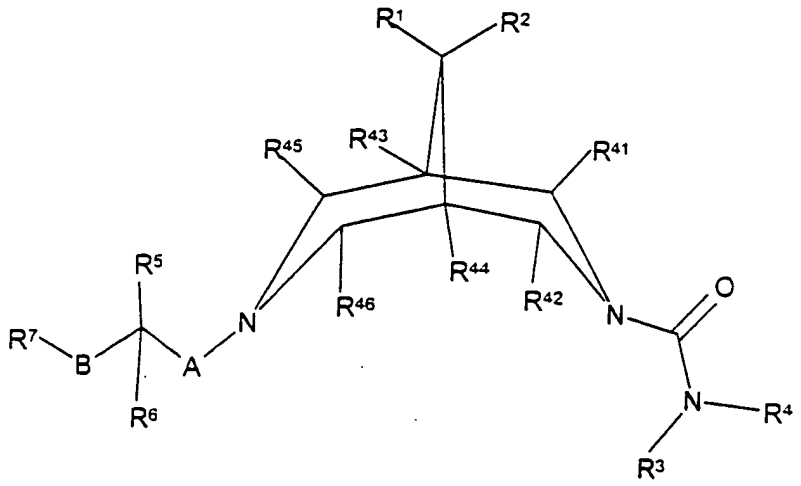
Antiarrhythmic drugs based on bispidines (3,7-diazabicyclo[3.3.1]nonanes), are known from *inter alia* international patent application WO 91/07405. European patent applications 306 871, 308 843 and [655 228] 665 228 and US patents 3,962,449, 4,556,662, 4,550,112, 4,459,301 and 5,468,858, as well as journal articles including *inter alia* J. Med. Chem. **39**, 2559, (1996), Pharmacol. Res., **24**, 149 (1991), Circulation, **90**, 2032 (1994) and Anal. Sci. **9**, 429, (1993). Known bispidine-based antiarrhythmic compounds include bisaramil (3-methyl-7-ethyl-9α,4'-(Cl-benzoyloxy)-3-7-diazabicyclo[3.3.1]nonane), tedisamil (3',7'-bis(cyclopropylmethyl)sipro-(cyclopentane-1,9')-3,7-diazabicyclo[3.3.1]nonane), SAZ-VII-22 (3-(4-chlorobenzoyl)-7-*iso*propyl-3,7-diazabicyclo[3.3.1]nonane), SAZ-VII-23 (3-benzoyl-7-*iso*-propyl-3,7-diazabicyclo[3.3.1]nonane), GLG-V-13 (3-[4-(1H-imidazol-l-yl)benzoyl]-7-*iso*-propyl-3,7-diazabicyclo[3.3.1]nonane), KMC-IV-84 (7[4'-(1H-imidazolo-1-yl)benzenesulfonyl]-3-*iso*-propyl-3,7-diazabicyclo[3.3.1]nonane dihydroperchlorate and ambasilide (3-(4-aminobenzoyl)-7-benzyl-3,7diazabicyclo[3.3.1]nonane).

IN THE CLAIMS

Please cancel Claims 19-23, without prejudice.

IN THE CLAIMS

1 (Amended). A compound of formula I,



I

wherein

R^1 and R^2 independently represent H, C_{1-4} alkyl, OR^{2b} or $N(R^{2c})R^{2d}$, or together form -O-$(CH_2)_2$-O-, -$(CH_2)_3$-, -$(CH_2)_4$- or -$(CH_2)_5$-;

R^{2b}, R^{2c} and R^{2d} independently represent H or C_{1-6} alkyl;

R^3 represents H, C_{1-6} alkyl or, together with R^4, represents C_{3-6} alkylene (which alkylene group is optionally interrupted by an O atom and/or is optionally substituted by one or more C_{1-3} alkyl groups);

R^4 represents H, C_{1-12} alkyl, C_{1-6} alkoxy (which latter two groups are both optionally substituted and/or terminated by one or more substituents selected from -OH, halo, cyano, nitro, C_{1-4} alkyl and/or C_{1-4} alkoxy), $-(CH_2)_q$-aryl, $-(CH_2)_q$-oxyaryl, $-(CH_2)_q$-Het^1 (which latter three groups are optionally substituted (at the $-(CH_2)_q-$ part and/or the aryl/Het^1 part) by one or more substituents selected from -OH, halo, cyano, nitro, $-C(O)R^{10}$, $-C(O)OR^{11}$, $-N(H)S(O)_2R^{11a}$, C_{1-6} alkyl and/or C_{1-6} alkoxy), $-(CH_2)_qN(H)C(O)R^8$, $-(CH_2)_qS(O)_2R^8$, $-(CH_2)_qC(O)R^8$, $-(CH_2)_qC(O)OR^8$, $-(CH_2)_qC(O)N(R^9)R^8$ or, together with R^3, represents C_{3-6} alkylene (which alkylene group is optionally interrupted by an O atom and/or is optionally substituted by one or more C_{1-3} alkyl groups);

q represents 0, 1, 2, 3, 4, 5 or 6;

R^8 represents H, C_{1-6} alkyl, aryl (which latter group is optionally substituted and/or terminated by one or more substituents selected from -OH, halo, cyano, nitro, $-C(O)R^{10}$, $-C(O)OR^{11}$, $-N(H)S(O)_2R^{11a}$, C_{1-6} alkyl and/or C_{1-6} alkoxy) or, together with R^9, represents C_{3-7} alkylene;

R^9 represents H, $C_{,4}$ alkyl or, together with R^8, represents C_{3-7} alkylene;

Het^1 represents a five to twelve-membered heterocyclic ring containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, and which also optionally includes one or more =O substituents;

R^{41}, R^{42}, R^{43}, R^{44}, R^{45} or R^{46} independently represent H or C_{1-3} alkyl;

R^5 represents H, halo, C_{1-3} alkyl, $-OR^{12}$, $-N(R^{13})R^{12}$ or, together with R^6, represents =O;

R^6 represents H, C_{1-4} alkyl or, together with R^5, represents =O;

R^{12} represents H, C_{1-6} alkyl, $-S(O)_2-C_{1-4}$-alkyl, $-C(O)R^{14}$, $-C(O)OR^{14}$, $-C(O)N(R^{15})R^{15a}$ or aryl (which latter group is optionally substituted and/or terminated by one or more substituents selected from -OH, halo, cyano, nitro, $-C(O)R^{10}$, $-C(O)OR^{11}$, $-N(H)S(O)_2R^{11a}$, C_{1-6} alkyl and/or C_{1-6} alkoxy);

R^{13} represents H or C_{1-4} alkyl;

R^{14} represents H or C_{1-6} alkyl;

R^{15} and R^{15a} independently represent H or C_{1-4} alkyl, or together represent C_{3-6} alkylene, optionally interrupted by an O atom;

A represents a single bond, C_{1-6} alkylene, $-N(R^{16})(CH_2)_r-$ or $-O(CH_2)_r-$ (in which two latter groups, the $-(CH_2)_r-$ group is attached to the bispidine nitrogen atom);

B represents a single bond, C_{1-4} alkylene, $-(CH_2)_nN(R^{17})-$, $-(CH_2)_nS(O)_p-$, $-(CH_2)_nO-$ (in which three latter groups, the $-(CH_2)_n-$ group is attached to the carbon atom bearing R^5 and R^6), $-C(O)N(R^{17})-$ (in which latter group, the -C(O)- group is attached to the carbon atom bearing R^5 and R^6), $-N(R^{17})C(O)O(CH_2)_n-$, $-N(R^{17})(CH_2)_n-$ (in which two latter groups, the $N(R^{17})$ group is attached to the carbon atom bearing R^5 and R^6) or $-(CH_2)_mC(H)(OH)(CH_2)_n-$ (in

which latter group, the $-(CH_2)_m-$ group is attached to the carbon atom bearing R^5 and R^6);

m represents 1, 2 or 3;

n and r independently represent 0, 1, 2, 3 or 4;

p represents 0, 1 or 2;

R^{16} and R^{17} independently represent H or C_{1-4} alkyl;

R^7 represents C_{1-6} alkyl, aryl or Het^2, all of which groups are optionally substituted and/or terminated (as appropriate) by one or more substituents selected from -OH, cyano, halo, amino, nitro, Het^3, $-C(O)R^{10}$, $C(O)OR^{11}$, C_{1-6} alkyl, C_{1-6} alkoxy, $-N(H)S(O)_2R^{18}$, $-S(O)_2R^{19}$, $-OS(O)_2R^{20}$, $-N(H)C(O)N(H)R^{21}$, $-C(O)N(H)R^{22}$ and/or aryl (which latter group is optionally substituted by one or more cyano groups);

Het^2 and Het^3 independently represent a five to twelve-membered heterocyclic group containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, and which also optionally includes one or more =O substituents;

R^{18}, R^{19} and R^{20} independently represent C_{1-6} alkyl;

R^{21} and R^{22} independently represent H or C_{1-6} alkyl (optionally terminated by cyano); and

R^{10} and R^{11} independently represent, at each individual occurrence, H or C_{1-6} alkyl;

R^{11a} represents, at each individual occurrence, C_{1-6} alkyl;

or a [pharmaceutically acceptable] salt, solvate or protected derivative thereof;

provided that:

(a) when A and B are both single bonds and R^7 is optionally substituted 10 aryl, then R^5 and R^6 do not both represent H;

(b) when A represents a single bond, then R^5 and R^6 do not together represent =O; and

(c) when R^5 represents -OR^{12} or -$N(R^{13})R^{12}$, then:-

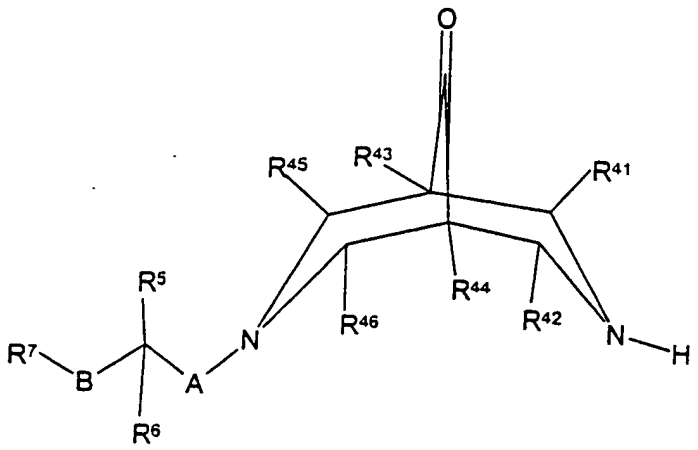
(i) A does not represent -$N(R^{16})(CH_2)_r$- or -$O(CH_2)_r$-; and/or

(ii) n does not represent 0 when B represents -$(CH_2)_nN(R^{17})$-, -$(CH_2)_nN(O)_p$- or -$(CH_2)_nO$-.

16 (Amended). A compound as claimed in Claim 15, wherein R^7 represents phenyl (substituted by a cyano group [(preferably in the 4-position relative to B)] and by one or more optional $C(O)N(H)R^{22}$ substituent).

26 (Amended). A compound of formula II, as defined in Claim 25, or a protected derivative thereof, provided that R^7 does not represent optionally substituted phenyl or C_{1-6} alkyl.

33 (Amended). A compound of formula XXIII,



XXIII

wherein R^5, R^6, [R^7,] R^{41}, R^{42}, R^{43}, R", R^{45}, R^{46}, A and B are as defined in Claim 1, R^7 represents aryl or Het^2, all of which groups are optionally substituted and/or terminated (as appropriate) by one or more substituents selected from ·OH, cyano, halo, amino, nitro, Het^3, $·C(O)R^{10}$, $C(O)OR^{11}$, C_{1-6} alkyl, C_{1-6} alkoxy, $·N(H)S(O)_2R^{18}$, $·S(O)_2R^{19}$, $·OS(O)_2R^{20}$, $·N(H)C(O)N(H)R^{21}$, $·C(O)N(H)R^{22}$ and/or aryl (which latter group is optionally substituted by one or more cyano groups); or a protected derivative thereof.